Dimethylethanolamine
[108-01-0]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

Dimethylethanolamine was selected by the NIEHS for nomination to the ICCEC based on its widespread use and exposure potential.

Dimethylethanolamine is synthesized from ethylene oxide and dimethylamine. The U.S. production of dimethylethanolamine was less than 5,005,000 lb (< 2270 metric tons [Mg]) in 1985. Chemical Week (1996) reported that the Huntsman Corporation would more than double its production of amines at the Conroe, TX, plant to 130 million lb/year (52,000 Mg/year) by August, 1997.

Dimethylethanolamine is used as a chemical intermediate for antihistamines and local anesthetics, as a catalyst for curing epoxy resins and polyurethanes, and as a corrosion inhibitor. It is also used as an amino resin stabilizer and as an intermediate in the synthesis of dyes, textiles, auxiliaries, and emulsifiers or solubilizers in water-based paints and coatings. Dimethylethanolamine salts such as *p*-acetamidobenzoate have been used in humans to treat central nervous system disorders believed to be associated with hypofunction of cholinergic neurons; in the treatment of learning and behavioral problems; hyperkinetic behavior; Huntington's chorea, tardive and levodopa-induced dyskinesias; chronic fatigue; and neurasthenia. The free base and its medicinal salts are widely advertised on the internet to enhance cognitive performance and other physiological functions by increasing acetylcholine concentrations in the brain.

Two industrial operations common in the U.S., spray-painting and beverage can lacquering, are potential emitters of the compound to the environment. The total number of U.S. workers exposed to dimethyl-ethanolamine was 33,474, of which 5559 were female.

In humans, 10-20 mg (0.042-0.084 mmol) of dimethylethanolamine tartrate, administered orally, produced mild mental stimulation. Larger doses (not specified) produced insomnia, muscle tenseness, and spontaneous muscle twitches. Doses of dimethylethanolamine as high as 1200 mg/day (13.46 mmol/day) have been reported to produce no serious side effects. Treatment with dimethylethanolamine for tardive dyskinesia was associated with serious cholinergic side effects, nasal and oral secretions, dyspnea, and respiratory failure. A worker developed severe respiratory symptoms, which seemed to be related to exposure to a spray paint containing dimethylethanolamine. In skin tests, high doses of dimethylethanolamine produced wheal and flare responses.

In human volunteers, 33% of an injected 1 g (10 mmol) dose of dimethyl-ethanolamine was excreted unchanged. It was suggested that the remaining dose could have been demethylated to ethanolamine and entered into normal metabolic pathways. In other mammals, it has been reported that dimethylethanolamine undergoes endogenous methylation.

When applied dermally to skin of rabbits dimethylethanolamine produced mild to severe irritation.

In rabbits orally administered a single dose of 1.0, 1.41, or 2.0 mL/kg (890, 1250, or 1800 mg/kg; 10, 14.0, or 20 mmol/kg) dimethylethanolamine, signs of toxicity were observed with the two higher doses.

In rabbits administered a single dose of 1.0, 2.0, or 4.0 mL/kg (890, 1800, or 3500 mg/kg; 10, 20, or 40 mmol/kg) dimethylethanolamine s.c., the two higher doses were toxic. Application of dimethylethanolamine to the eyes of rabbits produced moderate to severe irritation.

When exposed by inhalation to 1668, 2408, or 3311 ppm (6081, 8779, or 12,070 mg/m^3; 68.22, 98.49, or 135.4 mmol/m^3) dimethylethanolamine for 4 hours, rats exhibited dose-related mortality. Among rats that were exposed to 98, 288, or 586 ppm (360, 1050, or 2140 mg/m^3; 4.00, 11.8, or 24.0 mmol/m^3) for 6 hours/day, for 9 exposures during an 11-day period, all high-dose and some mid-dose rats died. In another study, rats were exposed to 8, 24, or 76 ppm (30, 87, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3) dimethylethanolamine for 6 hours/day, 5 days/week for 13 weeks. In mid- and high-dose rats, corneal opacity occurred. Histopathologic examination revealed changes in nasal tissue in high-dose rats, and to a much lesser degree, in mid-dose rats.

In pregnant Sprague-Dawley rats fed a choline deficient (CD) diet containing 1% dimethylethanolamine (10,000 mg/kg feed; 110 mmol/kg feed) from the 6th day of pregnancy until 2 weeks after delivery, only 18/253 offspring survived for more than 36 hours after birth, while all offspring of control rats survived at least 15 days.

There was no statistically significant increase in the incidence of neoplasms in any organ in female C3H/HeN mice given drinking water with 10 mM dimethylethanolamine for 105 weeks, or in female C3H/HeJ(+) mice given 15 mM dimethylethanolamine for 123 weeks.

Dimethylethanolamine was negative for mutation induction in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 both in the presence and absence of S9. It was also negative for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*. Dimethylethanolamine was found to induce DNA synthesis *in vitro* in NIH 3T3 clone-7 fibroblasts and to greatly enhance the mitogenic effect of insulin.

Dimethylethanolamine was negative *in vitro* for its ability to covalently derivatize protein, a process which enables some low-molecular-weight chemicals (LMWC) to induce allergic antibody-mediated responses which may cause asthma in people occupationally exposed to LMWC.

A chemical mixture containing 8% dimethylethanolamine, ~ 47% isobutyl alcohol, and 42% ethanol, 2-(dimethylamino,4-methylbenzenesulfonate) (salt) caused ocular, but not dermal, irritation in rabbits.

Di- and triaminoethanols, which are structurally related to dimethyl-ethanolamine, can give rise to *N*-nitrosodiethanolamine (NDELA) via nitrosation resulting from reaction with nitrite or nitrous oxide. NDELA is a potent carcinogen, and if dimethylethanolamine hypothetically was similarly nitrosated, the resulting nitrosamine might be carcinogenic.

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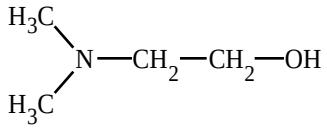
1.0 BASIS OF NOMINATION TO THE ICCEC

Dimethylethanolamine was selected by the NIEHS for nomination to the ICCEC based on its widespread use and exposure potential.

2.0 IDENTIFICATION AND CLASSIFICATION

Dimethylethanolamine
[108-01-0]



2.1 Chemical Identification

Dimethylethanolamine ($C_4H_{11}NO$, mol. wt. = 89.14) is also called:

Ethanol, 2-(dimethylamino)-(8CI9CI)
Amietol M 21
Bimanol
Deanol
(Dimethylamino)ethanol
2-(Dimethylamino)ethanol
2-(Dimethylamino)-1-ethanol
2-(*N*,*N*-Dimethylamino)ethanol
N-(Dimethylamino)ethanol
N,*N*-Dimethylaminoethanol
N,*N*-Dimethyl-2-aminoethanol
β-(Dimethylamino)ethanol
β-(Dimethylamino)ethyl alcohol
Dimethylethanolamine
N-Dimethylethanolamine
N,*N*-Dimethylethanolamine
Dimethyl(hydroxyethyl)amine
Dimethyl(2-hydroxyethyl)amine
N,*N*-Dimethyl(2-hydroxyethyl)amine
N,*N*-Dimethyl-*N*-(2-hydroxyethyl)amine
N,*N*-Dimethyl-*N*-(β-hydroxyethyl)amine
Dimethylmonoethanolamine
DMAE
Ethanolamine,
dimethyl-(2-Hydroxyethyl)dimethylamine
N-(2-Hydroxyethyl)dimethylamine
β-Hydroxyethyldimethylamine

Kalpur P	Norcholine
Liparon	Propamine A

Dimethylethanolamine has the designation for shipping UN 2051.

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Liquid	Budavari (1996)
Color	Colorless	HSDB (1996)
Melting Point, °C	-59	HSDB (1996)
Boiling Point, °C	134	Weast and Astle (1980)
Odor	Amine Odor	HSDB (1996)
Density at 20°C/4°C	0.8866	Weast and Astle (1980)
Solubility:		
Water	Soluble	Weast and Astle (1980)
Organic Solvents	Soluble in: ethanol, diethyl ether	Weast and Astle (1980)

Dimethylethanolamine is moderately flammable and is normally stable (HSDB, 1996). It is corrosive to skin and mucous membranes.

2.3 Commercial Availability

Bulk quantities of dimethylethanolamine are available from four suppliers in the United States - Ashland Chemical Co., Industrial Chemical and Solvents Division; BASF Corporation; Elf Atochem, North America, Inc., and Union Carbide Corporation. Elf Atochem supplies the compound in tank cars, tank trucks, 55-gal drums, and 5-gal pails (Strum, 1997).

3.0 COMMERCIAL PRODUCTION PROCESS

Dimethylethanolamine is synthesized from equimolar amounts of ethylene oxide and dimethylamine (Budavari, 1996).

4.0 PRODUCTION AND IMPORT VOLUMES

The U.S. production of dimethylethanolamine was 3,528,000 lb (1600 metric tons [Mg]) in 1972, 7,056,000 lb (3200 Mg) in 1977, and less than 5,005,000 lb (< 2270 Mg) in 1985 (HSDB, 1996).

In 1996, SRI International listed Elf Atochem North America, Inc., Huntsman Corporation, and Pelron Corporation as U.S. producers of dimethylethanolamine. Chemical Week (Anonymous, 1996) reported that the Huntsman Corporation would more than double its production of amines at the Conroe, TX, plant to 130 million lb/year (52,000 Mg/year) by August, 1997.

5.0 USES

Dimethylethanolamine is used as a chemical intermediate for antihistamines and local anesthetics, as a catalyst for curing epoxy resins and polyurethanes, and as a pH control agent for boiler water treatment (corrosion inhibitor) (HSDB, 1996). In addition, it is used as an amino resin stabilizer and as an intermediate in the synthesis of dyes, textiles, auxiliaries, and emulsifiers or solubilizer in water-based paints and coatings.

Dimethylethanolamine salts such as *p*-acetamidobenzoate (Deaner®; Pabenol) have been used in humans to treat central nervous system disorders believed to be associated with hypofunction of cholinergic neurons; in the treatment of learning and behavioral problems; hyperkinetic behavior (Stenbäck et al., 1988); Huntington's chorea (average daily dose for adults 1.0-1.5 g; 3.7-5.6 mmol), tardive and levodopa-induced dyskinesias (De Silva, 1977) (for case reports see **Section 9.1.1.2**); chronic fatigue; and neurasthenia (American Hospital Formulary Service, 1984; cited by HSDB, 1996). Other salts used included the aceglumate (Clérégil; Risatarun); the bitartrate (Liparon); and the hemisuccinate (Tonibral; Rishiaril) (Budavari, 1996). None of these salts were listed in the 1995 Physicians' Desk Reference, so they are apparently no longer widely prescribed as prescription drugs. However, the free base and its medicinal salts

are widely advertised on the internet to enhance cognitive performance and other physiological functions by increasing acetylcholine concentrations in the brain. For example, En Garde Health Products (1997) markets a buffered aqueous solution of dimethylethanolamine. Typical doses are up to 20 drops (50 mg) twice daily for adults and 10 drops (25 mg) daily for children. An approximate 2-month supply is equivalent to 2.3 oz. (70 mL; 200 drops). The company claims the solution enhances production of acetylcholine; sharpens concentration and memory; enhances muscle strength and coordination; improves mood; and fights fatigue.

The principal contraindication to use of dimethylethanolamine is grand mal epilepsy. Dimethylethanolamine also antagonizes the depressant effects of barbiturates (Gosselin et al., 1976).

6.0 ENVIRONMENTAL OCCURRENCE

No information on the environmental occurrence in the U.S. was found. However, two industrial operations common in the U.S., spray-painting and beverage can lacquering, are potential emitters of the compound to the environment. Environmental releases to the atmosphere of dimethylethanolamine might be expected from paint-spraying operations as suggested by the research conducted by the Statewide Air Pollution Research Center, University of California, which studied the potential for photooxidation of the compound (Pitts et al., 1980). Dimethyl-ethanolamine released in wastewater from washout to control emissions from water-based paint spray booths has been shown to be completely biodegraded by activated sludge bacteria (Stemad et al., 1995). In the U.K., dimethylethanolamine has been identified as one of the major odoriferous components from the ovens drying beverage cans after coating with solvent-borne and water-borne lacquers (Casper and Redman, 1995).

7.0 HUMAN EXPOSURE

The total number of U.S. workers exposed to dimethylethanolamine was 33,474, of which 5559 were female (NIOSH, 1984). See **Table 1** for data on exposure by occupation, and **Table 2** for data on exposure by industry.

Table 1. National Occupational Exposure Survey (NOES)[a]: By Occupation

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Assemblers	216	4995	2286
Automobile Mechanics	38	115	
Biological Technicians	21	686	300
Brickmasons and Stonemasons	12	108	
Carpenters	327	3435	
Chemical Technicians	119	953	259
Chemists, except Biochemists	17	1344	255
Clinical Laboratory Technologists and Technicians	26	59	33
Construction Laborers	5	1714	5
Electrical and Electronic Equipment Assemblers	31	31	
Electricians	17	487	6
Engineering Technicians, N.E.C.	19	190	57
Grinding, Abrading, Buffing, and Polishing Machine Operators	3	9	
Hand Molders and Shapers, except Jewelers	22	87	65
Janitors and Cleaners	97	737	
Laborers, except Construction Workers	146	1061	46
Machine Operators, not provided	27	128	
Machinists	33	295	
Managers and Administrators, N.E.C.	300	300	
Metal Plating Machine Operators	14	43	
Millwrights	3	16	
Miscellaneous Precision Workers, N.E.C.	3	494	
Miscellaneous Metal and Plastic Processing Machine Operators	22	1488	306
Miscellaneous Woodworking Machine Operators	7	62	7
Miscellaneous Machine Operators, N.E.C.	92	2172	154
Miscellaneous Material Moving Equipment Operators	50	101	
Mixing and Blending Machine Operators	88	1589	108
Painting and Paint Spraying Machine Operators	453	1824	64

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Printing Machine Operators	240	2393	850
Separating, Filtering, and Clarifying Machine Operators	201	4125	524
Stock and Inventory Clerks	19	37	
Supervisors, Production Occupations	127	713	
Technicians, N.E.C.	3	6	
Therapists, N.E.C.	73	219	219
Unspecified Mechanics and Repairers	14	710	14
Welders and Cutters	21	751	
TOTAL	2906	33,474	5559

[a]NIOSH (1984)
Abbreviations: N.E.C. = not elsewhere classified.

Table 2. National Occupational Exposure Survey (NOES)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Auto Repair, Services, and Garages	300	899	
Business Services	65	2016	639
Chemicals and Allied Products	197	10,096	1343
Electric, Gas, and Sanitary Services	38	115	
Electrical and Electronic Equipment	91	5624	1985
Fabricated Metal Products	65	535	
Food and Kindred Products	26	724	
Furniture and Fixtures	65	520	260
General Building Contractors	12	2033	5
Health Services	99	284	252
Instruments and Related Products	28	85	
Lumber and Wood Products	88	2256	7
Machinery, except Electrical	171	571	
Miscellaneous Manufacturing Industries	28	107	79
Paper and Allied Products	33	131	
Petroleum and Coal Products	21	1233	85
Primary Metal Industries	48	1383	14
Printing and Publishing	136	1364	818
Rubber and Misc. Plastics Products	67	713	64
Special Trade Contractors	246	2216	

Industry	Number of Plants	Number of Employees	Number of Female Employees
Transportation Equipment	13	568	7
TOTAL	1838	33,474	5559

[a]NIOSH (1984)

8.0 REGULATORY STATUS

	Regulation	Effect of Regulation/Other Comments
EPA	40 CFR 63. National Emission Standards For Hazardous Air Pollutants For Source Categories.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the Clean Air Act.
	40 CFR 63.100ff. Subpart F-National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry.	Chemical manufacturing process units that manufacture dimethylethanolamine or mixtures containing the compound are regulated under this subpart when produced at a plant site that is a major source as defined in section 112(a) of the Clean Air Act.
FDA	21 CFR 175. Indirect Food Additives: Adhesives and Components of Coatings.	§175.105 (Adhesives) regulates polyurethane resins produced by reacting *m*-tetramethylxylene diisocyanate with dimethylethanolamine. §175.300 (Resinous and Polymeric Coatings) states that dimethylethanolamine may be used as an optional adjuvant substance limited to no more than 2 wt. % based on polymer solids in the coating emulsion.

9.0 TOXICOLOGICAL DATA

Summary: In humans, 10-20 mg (0.042-0.084 mmol) dimethylethanolamine tartrate, administered orally, produced mild mental stimulation; larger doses produced insomnia, muscle tenseness, and muscle twitches. Treatment with dimethylethanolamine for tardive dyskinesia was associated with serious cholinergic side effects, nasal and oral secretions, dyspnea, and respiratory failure. A worker developed severe respiratory symptoms, probably related to exposure to paint containing dimethylethanolamine. In skin tests, high doses of dimethylethanolamine produced wheal and flare responses. In human volunteers, 33% of an injected 1 g (10 mmol) dose of dimethylethanolamine was excreted unchanged. It was suggested that the remaining dose could have been demethylated to ethanolamine and entered into normal metabolic pathways. In other mammals, dimethylethanolamine undergoes endogenous methylation.

Dermal and ocular application of dimethylethanolamine produced irritation in rabbits. In rabbits orally administered a single dose of 1.0, 1.41, or 2.0 mL/kg (890, 1250, or 1800 mg/kg; 10, 14.0, or 20 mmol/kg) dimethylethanolamine, toxicity was observed with the two higher doses. In rabbits injected s.c. with a single dose of 1.0, 2.0, or 4.0 mL/kg (890, 1800, or 3500 mg/kg; 10, 20, or 40 mmol/kg) dimethylethanolamine, the two higher doses were toxic. When exposed by inhalation to 1668, 2408, or 3311 ppm (6081, 8779, or 12,070 mg/m^3; 68.22, 98.49, or 135.4 mmol/m^3) dimethylethanolamine for 4 hours, rats exhibited dose-related mortality. Among rats that were exposed to 98, 288, or 586 ppm (360, 1050, or 2140 mg/m^3; 4.00, 11.8, or 24.0 mmol/m^3) for 6 hours/day, for 9 exposures, all high-dose and some mid-dose rats died. Corneal opacity and changes in nasal tissue were observed in rats exposed to 24 or 76 ppm (87 or 280 mg/m^3; 0.98, or 3.1 mmol/m^3) 6 hours/day, for 13 weeks. These effects were not present in rats exposed to a lower dose (8 ppm [30 mg/m^3; 0.3 mmol/m^3]). In pregnant rats fed a choline deficient (CD) diet containing 1% dimethylethanolamine (10,000 mg/kg feed; 110 mmol/kg feed) from the 6th day of pregnancy until 2 weeks after delivery, only 18/253 offspring of rats exposed to dimethyl-ethanolamine survived for more than 36 hours after birth, while all offspring of control rats survived at least 15 days.

There was no increase in the incidence of neoplasms in any organ in female C3H/HeN mice given drinking water with 10 mM dimethylethanolamine for 105 weeks, or in female C3H/HeJ(+) mice given 15 mM dimethylethanolamine in drinking water for 123 weeks.

Dimethylethanolamine was negative for mutation induction in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 both in the presence and absence of S9, for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*, and for the ability to covalently derivatize protein. Dimethylethanolamine induced DNA synthesis in fibroblasts and greatly enhanced the mitogenic effect of insulin.

A chemical mixture containing 8% dimethylethanolamine caused ocular, but not dermal, irritation in rabbits.

Di- and triaminoethanols, which are structurally related to dimethylethanolamine, can give rise to *N*-nitrosodiethanolamine (NDELA) via nitrosation. NDELA is a potent carcinogen, and if dimethylethanolamine were similarly nitrosated, the resulting nitrosamine might be carcinogenic.

9.1 General Toxicology

9.1.1 Human Data

9.1.1.1 Reviews

Pfeiffer et al. (1957; cited by Beard and Noe, 1981) reported that in humans, 10-20 mg (0.042-0.084 mmol) of the tartrate salt of dimethylethanolamine, administered orally, produced mild mental stimulation. At 20 mg/day (0.084 mmol), there was a gradual increase in muscle tone and perhaps an increased frequency of convulsions in susceptible individuals. Larger doses (amount not provided) produced insomnia, muscle tenseness, and spontaneous muscle twitches.

Gosselin et al. (1976) reported that doses of dimethylethanolamine as high as 1200 mg/day (13.46 mmol/day) produced no serious side effects. A single 2500-mg (28.05-mmol) dose taken in a suicide attempt had no adverse effect.

9.1.1.2 Case Reports

Treatment with dimethylethanolamine for tardive dyskinesia was associated with serious cholinergic side effects; nasal and oral secretions, dyspnea, and respiratory failure (Mehta et al., 1976; Nesse and Carroll, 1976). Dimethylethanolamine was used in the treatment of one patient for a low-frequency action tremor. This treatment was successful for 10 years, until side effects of increasing neck pain and orofacial and respiratory dyskinesia occurred. Dimethylethanolamine treatment was discontinued, and it was concluded that the dyskinesia could be attributed to the effect of dimethylethanolamine (Haug and Holzgraefe, 1991). A spray painter developed severe respiratory symptoms, which seemed to be related to the exposure of a specific type of spray paint containing dimethylethanolamine (Vallieres et al., 1977).

9.1.2 Metabolism

For identification of metabolites of dimethylethanolamine see **Table 3**.

9.1.2.1 Humans

In humans, 33% of an injected 1 g (10 mmol) dose of dimethylethanolamine was excreted unchanged (Williams, 1959; cited by Beard and Noe, 1981). It was suggested that the remaining dose could have been demethylated to ethanolamine and entered into normal metabolic pathways.

Dimethylethanolamine supplies the brain with choline, which is then acetylated by choline acetylase to form acetylcholine (De Silva, 1977). The effect of dimethylethanolamine on choline and acetylcholine levels in the brain may be the result of the increase in blood choline, and the

Table 3. Metabolites of Dimethylethanolamine

Metabolite Name	Experimental Details	Enzymes	Comments	Reference
Human				
dimethylethanolamine	33% of an injected 1-g (10-mmol) dose of dimethylethanolamine was excreted unchanged.	n.p.	The fate of the remaining dose was not determined, but the authors suggested that it could have been demethylated to ethanolamine and thus entered the normal metabolic pathways	Williams (1959; cited by Beard and Noe, 1981)
Mouse				
phosphoryldimethylethanolamine	Produced in brains of mice (strain not specified) administered [^{14}C]-dimethylethanolamine intracerebrally.	n.p.	Acid-soluble and lipid cholines derived from dimethylethanolamine were also produced.	Miyazaki et al. (1976; cited by Schlenk, 1990)
phosphatidyldimethylethanolamine				
Rat				
phosphoryldimethylethanolamine	n.p.	n.p.	[^{14}C]-Dimethylethanolamine was metabolized in the phospholipid cycle.	Dormand et al. (1975; cited by Schlenk, 1990)
glycerophosphatidylcholine				
unidentified substance; see "Comments"	n.p.	n.p.	Dimethylethanolamine "was converted to a substance which cross-reacted in the radioenzymatic assay for acetylcholine." Rats were kainic-acid lesioned.	London et al. (1978; cited by Schlenk, 1990)

Abbreviations: n.p. = not provided

suppression in choline uptake that it induces (Millington et al., 1978; cited by HSDB, 1996).

9.1.2.2 Other Mammals

It has been reported that dimethylethanolamine undergoes endogenous methylation (LaDu et al., 1971; cited by HSDB, 1996).

In mice (strain not provided) intravenous (i.v.) treatment with [^{14}C]dimethylethanolamine (dose not provided) in the brain yielded phosphoryldimethylethanolamine and phosphatidyldimethylethanolamine, along with acid-soluble and lipid cholines derived from dimethylethanolamine (Miyazaki et al., 1976; cited by Schlenk, 1990).

In rats (strain not provided), [^{14}C]dimethylethanolamine (dose not provided) was metabolized in the phospholipid cycle to produce phosphoryldimethylethanolamine and glycerophosphatidylcholine (Dormand et al., 1975; cited by Schlenk, 1990).

In rats (strain not provided), [^{14}C]dimethylethanolamine injected intracerebrally disappeared rapidly (Ansell and Spanner, 1979; cited by Schlenk, 1990). Concentrations of phosphatidylethanolamine increased continuously throughout the 7-hour observation period. When [^{14}C]dimethylethanolamine was injected i.p., the brain content of phosphatidylethanolamine increased throughout the 7-hour observation period and the levels were 10- to 40-fold higher than those of phosphodimethylethanolamine.

In kainic-acid lesioned rats (strain not provided), dimethylethanolamine (dose not provided) was converted to a substance that cross-reacted in the radioenzymatic assay for acetylcholine (London et al., 1978; cited by Schlenk, 1990).

In a study conducted by Haubrich et al. (1981; cited by HSDB, 1996), administration of dimethylethanolamine to mice increased both the concentration and rate of turnover of free choline in blood and kidneys (dose, route of administration, and mouse species and age were not provided).

Naujokaitis et al. (1984) conducted a study on the ability of dimethylethanolamine and some of its analogues to inhibit choline uptake in murine L1210 leukemia cells. Dimethylethanolamine (200 µM for 20 min) was found to be the most potent inhibitor of choline uptake.

9.1.3 Acute Exposures

The acute toxicity values for dimethylethanolamine are presented in **Table 4**. Other acute toxicity data are presented in **Table 5**.

Table 4. Acute Toxicity Values for Dimethylethanolamine

Route	Species, Strain, Sex	LD_{50} Value	Reference
dermal	rabbit	1.37 mL/kg (1210 mg/kg; 13.6 mmol/kg)	AMA Arch. Indust. Hyg. Occup. Med. (1951; cited by RTECS, 1996)
inhalation	mouse	3250 mg/m^3 (36.46 mmol/m^3)	Labor Hyg. Occup. Dis. (1970; cited by RTECS, 1996)
	rat (Wistar)	1641 ppm (5983 mg/m^3; 67.12 mmol/m^3)	Klonne et al. (1987)
i.p.	mouse	234 mg/kg (2.62 mmol/kg)	J. Pharmacol. Exp. Ther. (1948; cited by RTECS, 1996)
	rat (male Sprague-Dawley)	1080 mg/kg (12.12 mmol/kg)	Hartung and Cornish (1968)
oral	rat	2340 mg/kg (26.25 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981)
	rat	2000 mg/kg (22.44 mmol/kg)	Zeitschrift Gesamte Hyg. Ihre Grenzgebiete (1974; cited by RTECS, 1996)
	rat (male Sprague-Dawley)	6000 mg/kg (67.31 mmol/kg)	Hartung and Cornish (1968)
	rabbit (male)	1.75 mL (1550 mg; 17.4 mmol)	Union Carbide (1986)
	rabbit (female)	1.36 mL (1210 mg; 13.5 mmol)	

Route	Species, Strain, Sex	LD_{50} Value	Reference
s.c.	mouse	961 mg/kg (10.8 mmol/kg)	Naunyn-Schmiedeberg's Archiv für Exper. Pathol. Pharmakol. (1955; cited by RTECS, 1996)
	rabbit (male)	1.87 mL/kg (1660 mg/kg; 18.6 mmol/kg)	Union Carbide (1986)
	rabbit (female)	2.14 mL/kg (1900 mg/kg; 21.3 mmol/kg)	
	rabbit	1370 mg/kg (15.37 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981)
LD_{Lo} Value			
i.p.	guinea pig	450 mg/kg (5.05 mmol/kg).	Proc. Soc. Exp. Biol. Med. (1954; cited by RTECS, 1996)

Abbreviations: LD_{Lo} = lowest lethal dose

Table 5. Acute Toxicity of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.3.1 Dermal Exposure						
rabbit (age and strain n.p.)	n.p.	dimethylethanolamine, purity n.p.	445 mg (4.99 mmol) on open skin	n.p.	The dose produced mild irritation.	Union Carbide (1971; cited by RTECS, 1996)
rabbit (age and strain n.p.)	exposed: 3 M, 3 F controls: n.p.	dimethylethanolamine, 99.8% pure	0.5 mL (400 mg; 5 mmol) applied to occluded skin	4 h; 14 days	All rabbits developed severe erythema, edema, and necrosis. Scabs appeared on 5/6 rabbits after 2-3 days, and on the 6th rabbit after 7 days. Ulceration was detected in 2/6 rabbits at 2 days. Erythema persisted on 3/6 rabbits after 14 days. Based on these results, dimethylethanolamine is classified as corrosive by DOT definition.	Union Carbide (1986)
9.1.3.2 Oral Exposure						
rat (age and strain n.p.)	exposed: 5 animals per dose (sex n.p.) controls: n.p.	dimethylethanolamine, 99.8% pure	1.0, 1.41, or 2.0 mL/kg (890, 1250, or 1800 mg/kg; 10, 14.0, or 20 mmol/kg)	single dose; 14 days	The mid and high doses were toxic. Signs of toxicity included sluggishness, discharge around the eyes and nose, kyphosis (abnormal bending of the spine), and prostration. Symptoms abated at 2-5 days in survivors. Necropsy revealed mottled and red lungs, dark fluid in stomach and intestine, and reddened stomach.	Union Carbide (1986)
9.1.3.3 Subcutaneous Injection						
rabbit (age and strain n.p.)	n.p.	dimethylethanolamine, 99.8% pure	1.0, 2.0, or 4.0 mL/kg (890, 1800, or 3500 mg/kg; 10, 20, or 40 mmol/kg)	single dose; 14 days	The mid and high doses were toxic. Signs of toxicity included erythema, edema, necrosis, ulceration, and scabs in dosed skin, as well as salivation, sluggishness (in 1 animal), labored breathing (in 1 animal), emaciation (in 2 animals), and prostration (in 2 animals). Gross pathological examination revealed red and mottled lungs, mottled livers (tan to red), red tracheas, and s.c. redness.	Union Carbide (1986)
9.1.3.4 Ocular Application						
rabbit (age and strain n.p.)	n.p.	dimethylethanolamine, purity n.p.	0.75 mg (0.0084 mmol)	n.p.	The dose produced severe irritation. No other details were given.	AMA Arch. Indust. Hyg. Occup. Med. (1951; cited by RTECS, 1996)
rabbit (age and strain n.p.)	exposed: 3 M, 3 F controls: n.p.	dimethylethanolamine, 99.8% pure	0.005 mL (4 mg; 0.05 mmol) applied to eye	single dose; 21 days	Moderate to severe corneal injury, iritis, severe conjunctival irritation (with necrosis) were detected in all rabbits. Other symptoms included pinpoint pupils, exophthalmos (bulging), irregular corneal shape, and vascularization. After 10 days, a thick white opaque coating covered the cornea of 2 eyes. Four of 6 eyes remained affected through 21 days.	Union Carbide (1986)
9.1.3.5 Inhalation Exposure						

Abbreviations: F = female; M = male; n.p. = not provided; s.c. = subcutaneously

Table 5. Acute Toxicity of Dimethylethanolamine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rat (Wistar albino; age n.p.)	exposed: 5M, 5F per dose controls: n.p.	dimethylethanolamine, ≥ 99% pure	1668, 2408, or 3311 ppm (6081, 8779, or 12,070 mg/m^3; 68.22, 98.49, or 135.4 mmol/m^3)	4 h; 14 days after termination of exposure	All exposure groups developed lacrimation, excessive salivation, ocular, oral, and nasal discharge and encrustation, respiratory difficulties, decreased motor activity, coordination loss, and swelling and bleeding of extremities (feet and nose) from excessive preening (high dose only). There was a substantial body-weight loss in all but one survivor on post-exposure day 7. Discolored lungs, liver, kidneys, and spleen were observed in rats that died and in 2 high-dose survivors. Survivors in the low and mid dose groups did not have exposure-related macroscopic lesions at the end of the 14-day observation period.	Klonne et al. (1987)

Abbreviations: F = female; M = male; n.p. = not provided; s.c. = subcutaneously

9.1.3.1 Dermal Exposure

Application of 445 mg (4.99 mmol) dimethylethanolamine to open skin of rabbits (strain and age not provided) produced mild irritation (Union Carbide, 1971; cited by RTECS, 1996). No other details were given. Application of 0.5 mL (400 mg; 5 mmol) dimethylethanolamine for 4 hours to occluded skin of 3 male and 3 female rabbits (strain and age not provided) produced severe erythema, edema, and necrosis in all animals following a 14-day observation period (Union Carbide, 1986). Scabs appeared on all rabbits; ulceration and erythema on about half.

9.1.3.2 Oral Exposure

In rats (strain and age not provided) orally administered a single dose of 1.0, 1.41, or 2.0 mL/kg (890, 1250, or 1800 mg/kg; 10, 14.0, or 20 mmol/kg) dimethylethanolamine, and observed for 14 days, signs of toxicity were observed with the two higher doses (Union Carbide, 1986). Toxic effects included sluggishness, discharge around the eyes and nose, kyphosis (abnormal bending of the spine), and prostration. Symptoms abated at between 2 and 5 days. In rabbits that died, death occurred in 1 day or less. Necropsy revealed mottled and red lungs, dark fluid in stomach and intestine, and reddened stomach.

9.1.3.3 Subcutaneous Injection

In rabbits (strain and age not provided) administered a single subcutaneous (s.c.) dose of 1.0, 2.0, or 4.0 mL/kg (890, 1800, or 3500 mg/kg; 10, 20, or 40 mmol/kg) dimethylethanolamine and observed for 14 days, signs of toxicity were observed with the two higher doses (Union Carbide, 1986). Toxic effects included erythema, edema, necrosis, ulceration, and scabs in dosed skin, as well as salivation, sluggishness, labored breathing, emaciation, and prostration . Most deaths occurred on day 1. Gross pathological examination revealed red and mottled lungs, mottled livers, red tracheas, and s.c. redness.

9.1.3.4 Ocular Application

Application of 0.75 mg (0.0084 mmol) dimethylethanolamine to the eyes of rabbits (strain and age not provided) produced severe irritation (AMIHBC, 1951; cited by RTECS, 1996).

Application of 0.005 mL (4 mg; 0.05 mmol) dimethylethanolamine to the eyes of male and female rabbits (strain and age not provided) produced moderate to severe corneal injury, iritis, and severe conjunctival irritation (with necrosis) in all animals (Union Carbide, 1986). Other signs detected included pinpoint pupils, exophthalmos (bulging), irregular corneal shape, and vascularization (incidences not provided).

9.1.3.5 Inhalation Exposure

In male and female Wistar rats that were exposed to 1668, 2408, or 3311 ppm (6081, 8779, or 12,070 mg/m^3; 68.22, 98.49, or 135.4 mmol/m^3) dimethylethanolamine for 4 hours and observed for 14 days, 5/10 low-dose, 7/10 mid-dose, and 8/10 high-dose rats died 1 to 12 days after exposure (Klonne et al., 1987). Rats from all exposure groups developed lacrimation; excessive salivation; ocular, oral, and nasal discharge and encrustation; respiratory difficulties; decreased motor activity; coordination loss, and swelling and bleeding of extremities (feet and nose) from excessive preening (high-dose only); and a substantial body-weight loss. Discolored lungs, liver, kidneys, and spleen were observed in rats that died and in 2 high-dose survivors. Survivors in the low- and mid-dose groups did not have exposure-related macroscopic lesions at the end of the 14-day observation period.

9.1.4 Short-term and Subchronic Exposures

Studies described in this section are presented in **Table 6**.

9.1.4.1 Dermal Exposure

Male and female New Zealand White rabbits treated dermally with dimethylethanolamine developed severe skin irritation (Hermansky et al., 1995). The highest dose administered was 2.0 mL/kg/day (1800 mg/kg/day; 20 mmol/kg/day). Two lower doses were also administered, but information on these doses was not provided. All rabbits received 9 applications on shaved dorsal skin over 11 days. Microscopic examination revealed no treatment-related effects in regions other than treated skin.

9.1.4.2 Inhalation Exposure

Among male and female F344 rats exposed to 98, 288, or 586 ppm (360, 1050, or 2140 mg/m^3; 4.0, 11.8, or 24.0 $mmol/m^3$) dimethylethanolamine for 6 hours/day, 5 days/week for 9 exposures during an 11-day period, all high-dose rats died on days 4-8, and 4/15 mid-dose males died on days 8-12 (Klonne et al., 1987). Signs of respiratory distress, ocular and nasal irritation, and corneal opacity were observed in mid- and high-dose rats. All mid-dose rats had conjunctivitis, and corneal opacity. The mean body weight, and some organ weights, were

Table 6. Short-term and Subchronic Toxicity of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.4.1 Dermal Exposure						
rabbit (New Zealand White; ≤ 20-wk-old)	exposed: 5-10 rabbits/sex/ group controls: 5-10 M and 5-10 F	dimethylethanolamine, purity n.p.	3 doses were used; the highest was 2.0 mL/kg/day (1800 mg/kg/day; 20 mmol/kg/day); the mid- and low-doses were not specified. All rabbits received 9 applications on skin over 11 days (5 daily, 6 h applications, followed by 2 non-treatment days, and then 4 more consecutive treatment days)	11 days; rabbits were sacrificed on the day after the final treatment	Dimethylethanolamine caused severe skin irritation. No mention was made of reaction of controls. There were no treatment-related microscopic findings in regions other than treated skin.	Hermansky et al. (1995)
9.1.4.2 Inhalation Exposure						
rat (F344; approx. 8-wk-old)	exposed: 10M, 10F per dose. controls: 10M, 10F	dimethylethanolamine, ≥ 99% pure	98, 288, or 586 ppm (360, 1050, or 2140 mg/m^3; 4.0, 11.8, or 24.0 mmol/m^3), 6 h/day, 5 days/wk for 9 exposures during an 11-day exposure period (no exposure on days 5 and 6)	11 days; all rats were killed on the morning after the last exposure or when moribund	All HD rats died before the end of the study and were not evaluated; 4/15 MD males died 8-12 days after initiation of exposure (MD F were not mentioned). Signs of respiratory distress, ocular and nasal irritation, and corneal opacity were observed in MD and HD rats. No exposure-related neurobehavioral effects were detected. The principal histologic lesions were detected in the upper respiratory tract of LD and MD rats and in the eyes of the MD group. Most of the serum chemistry, hematology, and urinalysis values for the MD group were significantly different from control values.	Klonne et al. (1987)

Table 6. Short-term and Subchronic Toxicity of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rat (F344; approx. 9-wk-old)	exposed: 20M, 20F per dose controls: 20 M, 20 F	dimethylethanolamine, ≥ 99% pure	8, 24, or 76 ppm (30, 87, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3), 6 h/day, 5 days/wk	13 wk; one-half of all rats per sex group were killed after at least 2 days of exposure during the 14th week of the study; the remaining rats were killed after 5 weeks of recovery.	In MD and HD rats, corneal opacity occurred at the end of the daily exposures, beginning ~ 2-3 wk after initiation of exposure. The opacity regressed during non-exposure periods. In the HD group there was also audible respiration. There were no exposure-related effects on the gross appearance of organs. Nasal tissue histopathologic conditions included rhinitis; squamous metaplasia; degeneration of respiratory epithelium; atrophy of olfactory epithelium; and microcysts in respiratory epithelium. The incidence and severity of these lesions were decreased at the end of the recovery period.	

Abbreviations: F = female; HD = high dose; LD = low dose; M = male; MD = mid dose; n.p. = not provided

significantly depressed in low- and mid-dose rats. The principal histologic lesions were detected in the upper respiratory tract of low-dose and mid-dose rats, and in the eyes (ranging from corneal edema to ulcerative keratitis) of mid-dose rats. A large variety of nasal tissue histopathologic conditions were observed in low- and mid-dose rats.

In another experiment, male and female F344 rats were exposed to 8, 24, or 76 ppm (30, 87, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3) dimethylethanolamine for 6 hours/day, 5 days/week for 13 weeks (Klonne et al., 1987). Half of the rats were killed after at least 2 days of exposure during the 14th week of the study. The remaining rats were killed after 5 weeks of recovery. In mid- and high-dose rats, corneal opacity occurred at the end of the daily exposures, beginning approximately at exposure week 2-3. This opacity regressed during night-time non-exposure periods. In the high-dose group there was also an increase of audible respiration. Histopathologic examination revealed changes in nasal tissue in high-dose rats, and to a much lesser degree, in mid-dose rats. Nasal conditions included rhinitis, squamous metaplasia, degeneration of respiratory epithelium, atrophy of olfactory epithelium, and microcysts in respiratory epithelium. Nasal lesions were limited to the anterior nasal cavity and the incidence and severity of these lesions decreased by the end of the recovery period.

9.1.5 Chronic Exposures

No chronic exposure data were found, other than that described in **Section 9.3**.

9.2 Reproduction and Development

Studies described in this section are presented in **Table 7.**

In a study conducted by Katyal and Lombardi (1978), pregnant Sprague-Dawley rats were fed a choline deficient (CD) diet containing 1% dimethylethanolamine (10,000 mg/kg feed; 110 mmol/kg feed) from the 6th day of pregnancy until 2 weeks after delivery. Pups were

observed for 1 week after delivery. Controls were fed either CD diet alone or a CD diet + 0.8% choline chloride (choline-supplemented [CS] diet). Pregnancy progressed to term equally well in rats fed the various diets. Litters of similar sizes were delivered, with pups having only small differences in body weight. However, only 18/253 offspring of rats exposed to dimethylethanolamine survived for more than 36 hours after birth, while all offspring of control rats survived at least 15 days. Statistical comparison was made to the group of offspring of rats fed CS diet. Statistical comparison was not made between the group of offspring of rats fed CD diet + dimethylethanolamine and the group of offspring of rats fed CD diet alone. The lungs were the

Table 7. Reproductive and Developmental Effects of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rat (pregnant Sprague-Dawley)	n.p.	dimethylethanolamine, purity n.p.	exposed received 1% (10,000 mg/kg feed; 110 mmol/kg feed) in choline-deficient (CD) diet controls were fed either CD diet alone or CD diet + 0.8% choline chloride (choline-supplemented [CS])	pregnant rats were exposed from the 6th day of pregnancy until 2 weeks after delivery; pups were observed for 1 wk after delivery	Pregnancy progressed to term equally well in rats fed the various diets. Litters of similar sizes were delivered. Only 18/253 offspring of rats exposed to dimethylethanolamine, however, survived for more than 36 h after birth, whereas all offspring of control rats survived at least 15 days. Statistical comparison was made to the group of offspring of rats fed CS diet. Statistical comparison was not made between the group of offspring of rats fed CD diet + dimethylethanolamine and the group of offspring of rats fed CD diet alone. The lungs were the only organ examined. The concentrations of sphingomyelins, phosphatidyl cholines, and disaturated phosphatidyl cholines in the lungs of offspring of rats fed CD diet and dimethylethanolamine concurrently, and the amount of surfactant extracted from the lungs of these pups, were lower than the concentrations in offspring of rats fed CS diet alone. These changes were accompanied with changes in the activities of certain enzymes involved in the synthesis of lung lecithins.	Katyal and Lombardi (1978)

Abbreviations: n.p. = not provided

only organ examined. The concentrations of sphingomyelins, phosphatidyl cholines, and disaturated phosphatidyl cholines in the lungs of offspring of rats fed CD diet and dimethylethanolamine concurrently, and the amount of surfactant extracted from the lungs of these pups, were lower than the concentrations in offspring of rats fed CS diet alone. These changes were accompanied with changes in the activities of certain enzymes involved in the synthesis of lung lecithins.

9.3 Carcinogenicity

The study described in this section is presented in **Table 8**.

There was no statistically significant increase, or morphological difference, in the incidence of neoplasms in any organ in female C3H/HeN mice given drinking water with 10 mM dimethylethanolamine for 105 weeks, or in female C3H/HeJ(+) mice given 15 mM dimethylethanolamine for 123 weeks (Stenbäck et al., 1988). No changes in the structure, appearance, or microscopic morphology of various organs were observed. Treatment with dimethylethanolamine did not affect survival, initial body weight gain, or mature body weight of either strain of mouse.

9.4 Genotoxicity

Studies described in this section are presented in **Table 9**.

9.4.1 Prokaryotic Systems

As reported by Murray and Cummins (1979), dimethylethanolamine at 100 µL/plate (995 µmol/plate) tested only in the absence of rat liver metabolic activation did not induce *his* gene mutations in *Salmonella typhimurium* strain TA100 .

Zeiger et al. (1987) also reported that dimethylethanolamine did not induce *his* gene

mutations in *S. typhimurium.* Strains TA1535, TA1537, TA98, and TA100 were exposed to doses ranging from 33 to 10,000 µg/plate (0.37 to 112.2 µmol/plate) using the pre-incubation method either in the presence or absence of 10% rat or hamster liver S9.

9.4.2 Eukaryotic Systems

Foureman et al. (1994) observed that dimethylethanolamine did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. Canton-S males were given a 3-day feeding

Table 8. Carcinogenicity of Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
mouse (C3H/HeN and C3H/HeJ(+); age n.p.)[1]	exposed: 60F C3H/HeN; 50F C3H/HeJ(+) controls: 60F C3H/HeN; 50F C3H/HeJ(+)	dimethylethanolamine, purity n.p.	10 mM (group 2) or 15 mM (group 4) in drinking water	105 wk (groups 1 and 2) or 123 wk (groups 3 and 4); mice were allowed to die of natural causes or were killed when moribund	Treatment with dimethylethanolamine did not affect survival or the initial body weight gain or mature body weight of either strain of mouse. No macroscopical or microscopical pathological changes were Only the extent of lipofuscin (brown pigmented lipid-containing granules representing residues of lysosomal digestion) appeared less distinct in the livers of mice in groups 2 and 4.	Stenbäck et al. (1988)

[1] C3H/HeN mice carry a dominantly expressed germinal mammary tumor provirus, Mtv-1; C3H/HeJ(+) mice also carry the exogenous milk-transmitted mammary tumor virus

Abbreviations: F = female; n.p. = not provided

Table 9. Genotoxicity of Dimethylethanolamine

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.4.1 Prokaryotic Systems							
Salmonella typhimurium strain TA100	*his* reverse gene mutations	-	dimethylethanolamine, purity n.p.	100 µL/plate (995 µmol/plate)	negative	No other experimental details were given.	Murray and Cummins (1979)
S. typhimurium strains TA1535, TA1537, TA98, and TA100	*his* reverse gene mutations	-/+ 10% rat or hamster S9	dimethylethanolamine, purity n.p.	33 to 10,000 µg/plate (0.37 to 112.2 µmol/plate)	negative	The pre-incubation method was used with and without rat or hamster liver S9.	Zeiger et al. (1987)
9.4.2 Eukaryotic Systems							
Drosophila melanogaster strains Canton-S males and *Basc* females	sex-linked recessive lethal mutations	+	dimethylethanolamine, purity n.p.	7200 ppm (units as reported by authors) for a 3-day feeding exposure or 8100 ppm via injection.	negative	No increase in sex-linked recessive lethals was observed.	Foureman et al. (1994)

Abbreviations: n.a. = not applicable; n.p. = not provided

exposure to 7200 ppm (units as reported by authors) dimethylethanolamine, or 8100 ppm dimethylethanolamine delivered via injection. No increase in total lethals was observed.

9.5 Immunotoxicity

In skin tests done on human volunteers, high doses of dimethylethanolamine (undiluted, and 1:10 and 1:100 dilutions in saline) produced wheal and flare responses. This was interpreted as an irritant response, and not a sign of immunotoxicity (Vallieres et al., 1977).

Dimethylethanolamine was negative *in vitro* for its ability to covalently derivatize protein (Gauggel et al., 1993). It is thought that the ability to covalently derivatize protein enables some low-molecular-weight chemicals (LMWC) to induce allergic antibody-mediated responses which may cause asthma in people occupationally exposed to LMWC.

9.6 Other Effects

9.6.1 Cell Proliferation

Studies described in this section are presented in **Table 10**.

The potential of dimethylethanolamine to induce DNA synthesis *in vitro* has been investigated. NIH 3T3 clone-7 fibroblasts were treated with 0.1, 0.25, 0.5, or 1 mM dimethylethanolamine for 17 hours, with the addition of [methyl-^{3}H]thymidine for the last hour (Kiss and Crilly, 1996). DNA-associated ^{3}H activity was measured; 0.5 and 1 mM dimethylethanolamine enhanced DNA synthesis 12- to 33-fold, respectively. When 500 nM insulin was added after the addition of dimethylethanolamine, it was shown to greatly enhance the modest (15- to 20-fold) mitogenic effect of insulin. The mitogenic effects of insulin and dimethylethanolamine were inhibited by both 100 nM wortmannin (55-60% inhibition) and 0.5 mM 8-bromo cyclic AMP (~90% inhibition), but not by the protein kinase C inhibitor GF 109203X (data not given).

In a related study (Kiss et al., 1996), NIH 3T3 clone-7 fibroblasts were treated with the protein kinase C inhibitor GF 109203X, followed by dimethylethanolamine (0.1, 0.25, 0.5, 1, or 2 mM) for 17 hours (Kiss et al., 1996). Dimethylethanolamine at a dose of 1 mM enhanced insulin-induced DNA synthesis ~ 8.4-fold. Detectable (~ 2-fold) enhancement of DNA synthesis occurred with 0.1 mM dimethylethanolamine alone, while maximal enhancement of DNA synthesis occurred with 1 mM dimethylethanolamine.

Table 10. Other Effects: Cell Proliferation

Test System	Biological Endpoint	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
NIH 3T3 clone-7 fibroblasts	stimulation of DNA synthesis	dimethylethanol-amine, purity n.p.	0.1, 0.25, 0.5, or 1 mM for 17 h	At concentrations of 0.5 and 1 mM, dimethylethanolamine enhanced DNA synthesis 12- to 33-fold, respectively, in the absence of insulin. Dimethylethanolamine also greatly enhanced the modest (15- to 20-fold) mitogenic effect of [500 nM] insulin. The mitogenic effects of insulin and dimethylethanolamine were inhibited by both 100 nM wortmannin (55-60% inhibition) and 0.5 mM 8-bromo cyclic AMP (~90% inhibition), but not by the protein kinase C inhibitor GF 109203X (data not given).	Fibroblasts were treated with dimethyl-ethanolamine for 20 min. and then some samples were also treated with insulin (500 nM) for 16 h. Incubations were continued in the presence of [methyl-^{3}H]thymidine (1.5 µCi/well) for 60 min.	Kiss and Crilly (1996)
NIH 3T3 clone-7 fibroblasts	stimulation of DNA synthesis	dimethylethanol-amine, purity n.p.	0.25, 0.5, 1, or 2 mM for 17 h	Dimethylethanolamine (1 mM) enhanced insulin-induced DNA synthesis ~ 8.4-fold. Detectable (~ 2-fold) enhancement of DNA synthesis occurred with 0.1 mM dimethylethanolamine. Maximal enhancement of DNA synthesis occurred with 1 mM dimethylethanolamine. At 2 mM, there was slightly less mitogenic activity.	Fibroblasts were treated first with GF 109203X and then with dimethylethanolamine for 1-40 min. (not specified further). Some samples were also treated with insulin (500 nM) for 16 h. Incubations were continued in the presence of [methyl-^{3}H]thymidine (1.0 µCi/well) for 60 min.	Kiss et al. (1996)

Abbreviations: n.p. = not provided

9.6.2 Toxicity of Complex Mixtures

The studies described in this section are presented in **Table 11**.

The dermal and ocular toxicity of a chemical mixture containing 8% dimethylethanolamine, ~ 47% isobutyl alcohol, and 42% ethanol,2-(dimethylamino,4-methylbenzenesulfonate) (salt) was evaluated in New Zealand albino rabbits (American Cyanamid, 1991). For the dermal study, the rabbits were administered 0.5 mL of the chemical mixture on 1 intact and 1 abraded site on clipped dorsal skin (1.0 mL total dose/rabbit; skin was occluded) for 4 hours. Rabbits were evaluated for irritation at 1, 24, 48, and 72 h post-exposure. On a scale of 0 to 4 (Draize dermal scoring method), the chemical mixture scored a 0 for dermal irritation.

For the ocular irritation study, each rabbit had 0.1 mL of the chemical mixture placed into the conjunctival sac of the left and right eyes. Twenty to 30 seconds post-exposure, the left eye was flushed with water; the right eye was not washed. Eyes were evaluated 1, 24, 48, and 72 hours, and 7 days post-exposure. Corneal opacity, iritis, and moderate to severe conjunctival irritation persisted through day 7 in washed and unwashed eyes.

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Stenbäck et al. (1988) noted that di- and triaminoethanols, which are structurally related to dimethylethanolamine and are found in cutting fluids, pesticides, and cosmetics, can give rise to *N*-nitrosodiethanolamine (NDELA) via nitrosation resulting from reaction with nitrite or nitrous oxide. The authors also noted that NDELA has been shown to be a potent carcinogen, producing mainly hepatocellular carcinomas in rats and epithelial neoplasms of the nasal cavity and trachea in hamsters. Based on these data, Stenbäck et al. (1988) suggested that "if [dimethylethanolamine] were similarly nitrosated, the resulting nitrosamine might be carcinogenic."

Table 11. Toxicity of Complex Mixtures Containing Dimethylethanolamine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rabbit (New Zealand albino; age n.p.)	exposed: 3 (sex n.p.; the same rabbits as in the ocular study below) controls: none	chemical mixture containing 8% dimethylethanolamine, ~ 47% isobutanol, 42% ethanol,2-(dimethylamino-,4-methylbenzenesulfonate) (salt)	0.5 mL of the chemical mixture was applied to 1 intact and 1 abraded site on clipped dorsal skin occluded (1.0 mL total dose/ rabbit).	4 h; rabbits were evaluated for irritation at 1, 24, 48, and 72 h post-exposure	At 1 h post-exposure, there was absent to slight erythema. At 24, 48, and 72 h post-exposure no erythema was detected. No edema was detected at any of the evaluation time points. On a scale of 0 to 4 (Draize dermal scoring method), the chemical mixture scored a 0 for dermal irritation.	American Cyanamid (1991)
rabbit (New Zealand albino; age n.p.)	exposed: 3 (sex n.p.; the same rabbits as in the dermal study above) controls: none	chemical mixture containing 8% dimethylethanolamine, ~ 47% isobutanol, 42% ethanol,2-(dimethylamino-,4-methylbenzenesulfonate) (salt)	0.1 mL of the chemical mixture was placed into the conjunctival sac of the left and right eye of each rabbit	20-30 second post-exposure, left eye was flushed with water. The right eye was not washed. Eyes were evaluated 1, 24, 48, and 72 h, and 7 days post-exposure.	Corneal opacity, iritis, and moderate to severe conjunctival irritation persisted through day 7 in washed and unwashed eyes.	American Cyanamid (1991)

Abbreviations: n.p. = not provided

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

158 DIOGENES
136 Federal Register Abstracts
229 Drug Information Fulltext

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CEN (Chemical & Engineering News)
CIN (Chemical Industry Notes)
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
PROMT (Predicasts Overview of Markets and Technology)
Registry File

RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

11.2 Secondary References

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